IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	)	
RICHARD J. CAWTHRAY ET AL.	:)	Examiner: Lezah Roberts
Application No.: 10/789,525	:)	Art Unit: 1612
Filed: February 27, 2004	:)	Confirmation No.: 7746
For: KIT FOR PHARMACEUTICAL USE	:)	

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION UNDER 37 C.F.R. §1.132

Sir:

Stefan Van Der Geest declares and says that:

1. I am a medical doctor working as a European medical expert in the treatment of osteoporosis. I received my medical degree from the Erasmus University in Rotterdam, the Netherlands, and a post graduate degree in pharmaceutical medicine from the Royal College of Physicians in the United Kingdom. I have worked in the field of research and development regarding osteoporosis for over 13 years.

2. I currently hold the position of Principal Scientist at Warner Chilcott Pharmaceuticals.

3. Along with the other named inventors, I invented and designed the blister pack of the above-identified application and am familiar with the prosecution of this patent

application. In particular, I am aware that the Examiner has alleged that the present claims are obvious over U.S. Patent No. 5,994,329 (Daifotis) in view of either U.S. Patent No. 4,817,819 (Kelly) or U.S. Patent No. 5,265,728 (Allendorf) and further in view of Palo Alto Medical Foundation, "Calcium and Nutrition PAMF Patient Health Information," January 2002 (Palo Alto Medical Foundation).

4. Osteoporosis becomes a significant issue for people when fractures in the bone occur. Often these fractures lead to disability and severe impairment of quality of life. I have spent most of my efforts in educating physicians on the need for treatment and on treating with the best and most suitable treatments. Osteoporosis treatment is meant to prevent fractures from occurring in the future. To achieve this, physicians should prescribe the most suitable medication. However, such medication can only work if patients comply with administration instructions and, because these medications need to be taken for long periods of time, patients must continue to comply for prolonged periods of time.

5. Bisphosphonates are established today as the gold standard for the treatment of postmenopausal osteoporosis. However, bioavailability of bisphosphonates is poor due to low intestinal absorption rates. In addition, food, calcium and other polyvalent cations further decrease the absorption of these drugs, due to complex formation. As a result, bisphosphonates should be taken on an empty stomach, to ensure unimpaired intestinal absorption. Accordingly, the intake of bisphosphonates is not simple.

6. Calcium and vitamin D supplementation are recommended with anti-resorptive therapy in all recently published national and international osteoporosis treatment guidelines. The aim of calcium supplementation, in combination with bisphosphonate treatment, is to ensure sufficient availability of calcium for bone matrix mineralization, calcium homeostasis and avoidance of secondary hyperparathyroidism.

7. The frequency of insufficient calcium intake is high and the average daily calcium supplementation needed for postmenopausal osteoporotic women varies between 400 mg to 650 mg. In all large bisphosphonate trials that I have conducted or reviewed, patients have received 500-1000 mg of calcium per day to supplement their normal dietary intake. The need for sufficient calcium intake is mentioned in the summaries of many product characteristics of antiresorptive osteoporosis drugs. Importantly, the therapeutic potential of bisphosphonates has only been demonstrated under optimal calcium intake.

8. Despite clear recommendations in osteoporosis guidelines, the co-prescription rate and/or calcium intake advice from physicians is suboptimal. As shown in Table 1, co-prescription rates of calcium or calcium/vitamin D, along with a bisphosphonate, in European countries reaches only 11% to 51%.

Table 1: Percentage of Co-prescription Rates of Calcium or Calcium/Vitamin D with Bisphosphonate

Country	Percentage of Co-prescriptions[1]
Germany	12%
UK	11%
France	46%
Italy	25%
Spain	51%

Many physicians tell the patient to buy an over the counter calcium supplement, but they stress insufficiently that this calcium is an essential part of the treatment of osteoporosis and should not be considered just a supplement considered an optional addition.

9. Although calcium and vitamin D are needed as part of an osteoporosis therapy, incorrect dosing of these products can lead to reduced efficacy or adverse events. A study has shown that when a bisphosphonate is taken concurrently with a calcium product, the

[1] Source: IMS data review 2003 on co-prescription of calcium or calcium/vitamin D and bisphosphonates.

bisphosphonate is completely ineffective, as measured by bone mineral density (BMD). Many physicians may not take the time to explain the dosing instructions appropriately and patients tend to take their medication in a way that best suits them, regardless of the instructions in patient information leaflets.

10. Approximately 60% of bisphosphonate users currently take a calcium-containing supplement. A survey has shown that 1 in 5 postmenopausal osteoporotic women take their calcium-containing nutrient and/or other medication incorrectly in relation to the bisphosphonate. As many as 10% took the calcium-containing nutrient and the bisphosphonate concurrently. In addition, the survey showed that 4% of patients took the bisphosphonate with some fluid other than water, and 5% took it with food. These findings demonstrate that patients often do not comply with the dosing instructions.

11. In sum, non-compliance with dosing instructions of bisphosphonates and calcium-containing supplements leads to insufficient separation of the two medications and lower absorption of the bisphosphonate with a risk of impaired treatment outcome. There is a need to create a better method and type of administration to increase the number of patients taking a combined treatment of bisphosphonate and a calcium-containing supplement, and the number of patients taking this combination correctly. Further, a method or administration is needed for patients which is less dependent on instructions by physicians and complex dosing instructions from 2 different information sheets.

12. The invention and availability of a better treatment was needed. The subject fixed combination pack of risedronate with calcium-containing nutrient specifically arranged to facilitate correct dosing will increase the likelihood that postmenopausal osteoporotic patients will receive both a calcium-containing nutrient and risedronate, thereby fulfilling this need in the market and providing superior treatment to patients in need. To address this, we

invented the blister card of the present invention (referred to in the test below as "combination pack"), which does not contain a calcium-containing tablet on the day of the bisphosphonate intake but, for the rest of the week, it contains 6 (or 12) calcium-containing tablets.

13. To demonstrate that the instructions of the combination pack (blister card of the subject invention) are more easily understood and therefore, the doses properly administered and the benefits of treatment increased, a study was performed under my direction and control. Full details of the study, which was conducted to compare the clarity and understandability of the dosing instructions of separate packs (treatment previously prescribed and known in the art where the bisphosphonate is in one pack and the calcium-containing supplement is in a second pack) with the dosing instructions of the combination pack, are set forth below.

Materials and Methods

- Description and dosage of the combination pack
    - The combination pack of the present invention contains 4 blisters. Each blister has 7 tablets, one of which is a risedronate 35 mg film-coated tablet and the remaining 6 are calcium carbonate 1250 mg film-coated tablets (500 mg elemental calcium) (Figure 1). Patients are advised to first take the risedronate tablet on a chosen day. Then, one calcium-containing tablet should be taken on each of the subsequent 6 days. This 7-day sequence is repeated each week for 4 weeks. The blister strip separates the risedronate and calcium-containing tablet and clearly indicates the sequence in which the tablets should be taken. Risedronate 35 mg/week has been shown to be therapeutically equivalent to risedronate 5 mg/day, a dose that is effective in the prevention and treatment of osteoporosis by reducing the risk of vertebral, non-vertebral, and hip fractures.

Patients and Study Design

- The test was performed in a cohort of 164 postmenopausal women at least aged 55 years (mean age 69 years) in the UK and Germany. Half of the participants (N=83) were selected on the basis of being current bisphosphonate users. All bisphosphonate users were asked before the test how they would normally take their bisphosphonate. The baseline characteristics are summarized in Table 2 below.

Table 2: Patient baseline characteristics	
Parameter / Statistic	[N=164]
Age (Years)	
≤60	40 (24%)
>60 - ≤65	27 (16%)
>65 - ≤70	33 (20%)
>70 - ≤75	19 (12%)
>75 - ≤80	30 (18%)
>80	15 (10%)
Mean (SD) Median Range	69 (8.8) 68 55-91
Previous Use Of Bisphosphonates	
Yes	83 (51%)
No	81 (49%)
Country	
UK	62 (38%)
Germany	102 (62%)

- A semi-structured questionnaire with 28 questions was used. Trained interviewers conducted face-to-face interviews during home visits, which lasted 30-40 minutes. The packs were given to the participants. Before answering the questions, participants had 10 minutes to read both packaging options. Participants were allowed to check the packaging before answering. The test used a crossover design, in which half of the participants were given the combination pack first followed by the current packaging (i.e., the separate pack), with the remaining patients given the current packaging first. The impact of the combination pack on the patients understanding of intake instructions was studied versus separate packs. Patient understanding of the following five dosing instructions was tested:

  1. Intake of risedronate in the morning
  2. Intake of risedronate only with water
  3. Intake of risedronate without food
  4. Intake of risedronate without other medication at the same time
  5. Intake of calcium separate from the risedronate

  In addition, the understanding of the instructions for the correct handling of a missed dose of risedronate was tested. Participants were asked for their preference for the combination packaging versus the separate packs.

Statistical Methods

- All of the 164 women who took part in the test were included in the analysis. Baseline characteristics were summarized using descriptive statistics. Formal statistical modeling was performed using SAS Version 9.1, and all statistical

tests were two-sided at the 5% level of significance. Formal statistical methods take into account the crossover design of the packaging test.

Results

- We evaluated the habits of patients currently taking a bisphosphonate. Sixty percent of the bisphosphonate users took a calcium supplement in addition to their bisphosphonate therapy and 10% of these patients took the calcium and the bisphosphonate at the same time of the day. Four percent of patients took the bisphosphonate with some fluid other than water and 5% took it with food. A total of 18% took their bisphosphonate together with other medication.
- Understanding of the dosing instructions
    - Analysis of the crossover data showed a significantly better understanding of the 5 instructions, taken together, for the combination package compared with the separate packs [82% versus 70%, $p<0.001$] (Figure 2).
    - In the patients that were shown the separate packs first, the percentage of participants with correct understanding of all five tested dosing instructions together increased from 67% to 88% after they were shown the fixed combination pack ($p<0.05$). This improvement was not due to improved understanding when patients read the instructions for a second time. When the combined pack was shown first, followed by the individual packs the understanding of all five dosing elements did not improve. In these patients, understanding was 76% after review of the fixed combination pack and 73% after the subsequent review of the individual packs ($p>0.05$).
- Correct understanding of dealing with a missed dose of risedronate
    - After crossover, the correct understanding of dealing with a missed dose of risedronate was observed in 79% of participants given the combination pack versus 68% of participants given the separate pack ($p<0.05$) (Figure 3).
- Opinion on instructions and packaging overall
    - The participants rating of the instructions with ease of understanding significantly favored ($p<0.001$) the combination pack compared to the separate packaging (Figure 4). Participants were more likely to have a favorable opinion of the combination pack overall compared to the separate packaging overall ($p<0.001$) (Figure 5).
- Preference and preference reasons
    - In the comparative packaging test, participants were asked for their preference and the reasons for this preference. Eighty-three percent of participants preferred the fixed combination pack over separate packs ($p<0.05$); Figure 6 shows the most frequently stated reasons for this preference and the overall patient preference for the combination pack over separate packages.

Conclusion

- The combination pack was preferred by the participants, over the same medication from separate packs. Participants better understood the dosing instructions of the combination pack and patients are, therefore, more likely to comply with the instructions and benefit from treatment.
- Our results indicate that the combination pack is perceived to simplify a complex therapy regime. Several authors have stated that simplification of therapy enhances adherence. Thus, simplification of therapy of a combined pack of risedronate and calcium-containing supplement is expected to lead to improved compliance and adherence to treatment.

14. In terms of calcium dosage, vitamin D and safety, the combination pack ensures supplementation of 500 mg calcium for 6 out of 7 days. Together with a typical European dietary intake, this should provide an appropriate calcium intake that is in line with guidelines for the treatment of osteoporosis. No specific disadvantages of the fixed combination pack have been identified, with the exception that a few patients may require still higher doses of calcium. For those few patients with an extremely low daily calcium intake, i.e., less than 400 mg calcium per day, it could be advisable to prescribe the combination pack supplemented by additional packs of calcium. There is no reason to expect any increased safety risks through use of the combination pack compared to treatment using separate packs.

15. In summary, through the study described above, I was able to demonstrate better understanding of the instructions of the subject invention, not least because, on the day of the bisphosphonate dose, there is no calcium or calcium/vitamin D dose. This in itself reduces the chances of simultaneous dosing. The blister pack of the present invention avoids simultaneous administration of bisphosphonates and calcium or calcium-containing nutrients while facilitating administration of, separately, bisphosphonates and calcium or calcium-containing nutrients.

16. For postmenopausal osteoporotic women, the expected benefits of the combination pack are:

- A treatment regimen that includes calcium-containing supplementation with prescription medicine, which increases the probability that patients will receive both calcium (with or without vitamin D) and risedronate.
- Improved patient understanding of dosing regimen to avoid incorrect intake, thereby leading to optimal absorption of risedronate and calcium (with or without vitamin D).

17. This invention aids patients in receiving better treatment for osteoporosis through intake of both a bisphosphonate and calcium-containing therapy in the correct manner of administration. Simplification of bisphosphonate and calcium-containing therapy in the combination pack of the subject invention, not disclosed or suggested in the prior art, leads to improved compliance and to better therapeutic outcome in terms of reducing the problems of osteoporosis, i.e., bone fractures.

I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the above-referenced application or any patent issuing thereon.

19 January 2011
Date

Stefan Van Der Geest

Figure 1: Blister strip containing one tablet of risedronate 35 mg and 6 calcium carbonate 1,250 mg (500 mg elemental calcium) tablets for a week of therapy

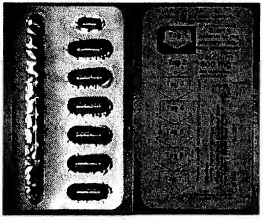

Figure 2: Correct understanding of intake instructions

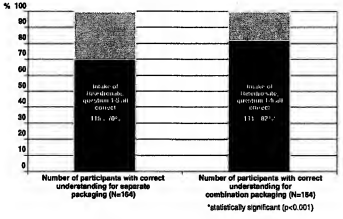

Figure 3: Correct understanding of instructions for a missed dose of risedronate

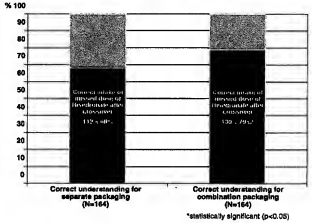

Figure 4: Rating of the overall ease of instructions

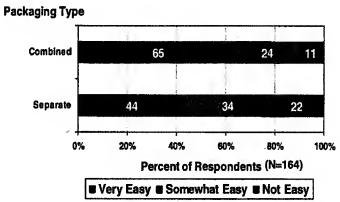

Figure 5: Overall rating of the packaging

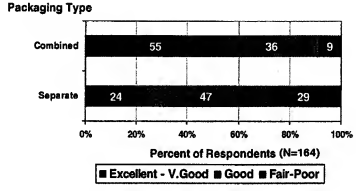

Figure 6: Overall patient preference for the combination package over separate packages (yellow bar) and reasons for patient preference for combination package (blue bar; multiple reasons could be given by participants)